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EXAMINER	
SCHUBERG, LAURA J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,974	PROSPER CARDOSO ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-67* is/are pending in the application.

4a) Of the above claim(s) *41-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 31-67 are currently pending.

Claims 41-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 31-40 have been amended. No claims have been newly added or canceled. Claims 31-40 have been examined on the merits.

Response to Arguments

Applicant's arguments filed 12/30/2008 have been fully considered but they are not persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicant argues that the restriction requirement is not proper and should be withdrawn. Applicant asserts that the claimed media composition greatly contributes to the technical advancement of the field of isolation and expansion of cultured autologous human progenitor stem cells. Applicant asserts that the Examiner has broadened the intended use beyond acceptable provisions provided by 37 CFR 1.475. Applicant asserts that the contribution is clearly defined throughout the Specification and the claims to the isolation and expansion of the progenitor stem cells.

This is not found persuasive because the common technical feature that the different inventions have in common is the composition of the culture media comprising components a-d. The feature regarding the intended use of the composition for the expansion of stem cells is not a feature that all the inventions have in common as several inventions do not recite any limitations with regard to expansion (see groups II, IV, V, VII, and VIII from the Restriction Requirement). However even if every invention required that the composition be an expansion media composition, the claimed composition would have still been an obvious variant of the Xia composition as it contains all the same components as the Xia and differs only in the concentration of the heparin component. Xia et al demonstrates that the heparin concentration is a result effective variable (page 1132, column 2 and page 1133, figure 2) and clearly subject to routine optimization and experimentation. As the composition is rendered obvious by the prior art it can not be a special technical feature and therefore unity of invention is lacking.

According to 37 CFR 1.476, lack of unity of invention may be directly evident before considering the claims in relation to any prior art, or after taking the prior art into consideration, as where a document discovered during the search shows the invention claimed in a generic or linking claim lacks novelty or is clearly obvious, leaving two or more claims joined thereby without a common inventive concept. Therefore a common technical feature which is an obvious variant of a known composition can not be a special technical feature and thus unity of invention is lacking.

Applicant argues that Xia provides an improper basis for the restriction requirement because Xia uses the media composition for different cell types for different reasons than Applicant's claimed inventions. Applicant asserts that because Xia uses the media composition with monocytes and dendritic cells and because the motivation of Xia to use heparin and protamine run contrary to that disclosed in the present application that Xia provides an improper basis for the restriction.

This is not found persuasive because the media composition as claimed is deemed to be an obvious composition based upon its structural features and components. The method steps for using the claimed composition are not given consideration when assessing the patentability of the composition. Therefore the type of cell that media composition is used with or the motivation for adding any ingredients are deemed to be irrelevant to the examination of the composition unless they require a structural form or feature to be present or absent in the claimed composition. Since the media composition of Xia is in a form suitable for use with autologous human progenitor stem cells, the media composition of Xia renders obvious Applicant's media composition as claimed. Evidence of this suitability is also found In Applicant's disclosure as amounts of heparin of up to 10,000 UI/ml are indicated as suitable (see abstract and page 3 paragraph 20 of the Specification). The restriction requirement is therefore deemed to be proper and final.

Applicant argues that the Specification at least implicitly defines "basic nutrients" to be furnished by the medium HAM F12 [GIBCO BRL] and cites pa. 2 paragraph 28 as evidence.

This is found partially persuasive as the Specification describes on page 4 paragraph 23 of the disclosure as filed that "in principle, any medium which provides the adequate nutrients for the cell culture can be used in the present invention". Therefore, given this disclosure, "basic nutrients" are interpreted to be those nutrients supplied by any media composition wherein cells have been successfully cultured.

Applicant argues that heparin is used in Xia as a differentiation factor. Applicant asserts that because Xia is concerned with differentiation and not concerned with the problem of expanding progenitor stem cell cultures, Xia is not in the field of endeavor of the present application. Applicant asserts that cell differentiation is a different field than cell expansion.

This is not found persuasive as those of skill in the art of maintaining and using cells for cell therapy are all concerned with optimizing culture conditions for the maintenance of cells. One of ordinary skill in the art of using cells for cell therapy requires knowledge and skill with regard to both expansion and differentiation of cells in order to obtain sufficient amounts and types of cells needed for therapeutic treatments. There is so much overlap required for the culture techniques of cell expansion and differentiation that they are most often performed by the same skilled artisan. In fact many references regarding stem cell therapy address both expansion and differentiation as both are required for the successful maintenance and administration of stem cells for therapeutic purposes. The patent of Peled et al (US 6,887,704) is drawn to methods of controlling proliferation **and** differentiation of stem and progenitor cells. Peled et al teach that following cell expansion, it is important to have methods to induce differentiation of

the expanded cell population, so as to convert the expanded cell population to mature functional cells or tissue (column 2 lines 37-40). Clearly both expansion and differentiation are so crucial to the use of stem cells that the artisan of skill in the art of using stem cells would be required to have knowledge of both processes in order to be able to successfully use the stem cells for therapeutic purposes. In addition, the overlap in requirements between an expansion media and a differentiation media is so much so that Xia's media used for differentiation is almost identical to the claimed media composition that is intended for expansion differing only in the concentration of one ingredient.

Applicant argues that differentiated cells cannot be expanded. Applicant asserts that those skilled in the art would not be motivated to use the knowledge in Xia for solving a cell expansion problem.

This is not found persuasive because those skilled in the art of cell culture are motivated to optimize media compositions to control the characteristics of the cell culture that they are maintaining. One of ordinary skill in the art of cell culture, especially for cell therapy purposes, would be motivated to use the knowledge in Xia as the ability to control the differentiation of cells by modifying media ingredients would be of value in the art of cell therapy. Also differentiated cells (such as fibroblasts), while not having unlimited expansion abilities, may indeed be expanded in culture for a limited time for therapeutic purposes (see Naughton et al US 5,863,531).

Applicant argues that claims 33-35 are not product-by-process claims because these claims do not recite a product. Applicant asserts that according to the

embodiment recited in claims 34-35, the process of obtaining the autologous serum is via plasmapheresis.

This is not found persuasive as claims 33-35 are all drawn to the expansion culture medium according to the claim 31 and further include limitations that indicate the manner in which one of the components was obtained (the autologous serum). These are therefore product by process limitations as they are drawn to how a composition is made and do not add any structural features or components to the claimed composition. Since it appears that the autologous serum in the Xia et al composition is not patentably distinct from Applicant's claimed autologous serum, they are deemed to be the same unless Applicant can provide some evidence that the autologous serums are somehow different.

Applicant argues that Xia et al provides no motivation to arrive at the same concentration of the product for the present invention.

This is not found persuasive because generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a

temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."). Since Applicant has disclosed that amounts of heparin of up to 10,000 UI/ml are suitable for the media composition (see abstract and page 3 paragraph 20 of the Specification) and Xia et al also disclose that the heparin concentration can be modified (figure 2 page 1133), it is deemed that one of ordinary skill in the art would have had sufficient motivation to lower the concentration of heparin to 10 U/ml as a lower concentration would save money and still provide an effective composition according to Xia et al's disclosure.

Applicant argues that Furcht does not disclose or suggest the use of autologous serum for any other purpose than to maintain the MASCs extracted from bone marrow. Applicant asserts that those skilled in the art would not obviate the use of autologous serum for reducing immune rejection based upon the entire disclosure of Furcht.

This is not found persuasive because the disclosure of Furcht is relied upon in the obviousness rejection to demonstrate that the culture media used to maintain cells can be supplied with either fetal calf serum, human serum or autologous serum. That these serums are in fact all suitable for use in a cell culture media and are to a certain extent art recognized equivalents as serum supplements for cell culture media. The motivation to choose the autologous serum from the list of suitable alternatives comes from the fact that Chachques emphasizes the importance of avoiding an immune

response by using autologous cells combined with the fact that Furcht et al also teaches that the same cells can be cultured with autologous serum as well as fetal calf serum. One of ordinary skill in the art would have had a reasonable expectation of success in combining these teachings because both Chachques and Furcht et al were culturing cardiac cells for the treatment of a damaged myocardium.

Applicant argues that because bone marrow cells are not the same type of cells exemplified in the present application which are muscle progenitor CD56+/CD45- cells, that Furcht does not relate to the same field of endeavor as the present application and the combination of Chachques and Furcht is misplaced. Applicant asserts that Valerio and Wilson are also improperly combined as they do not relate to the same field of endeavor as Applicant.

This is not found persuasive because the claims are broadly drawn to an expansion culture medium that is suitable for the expansion of autologous human progenitor stem cells and the actual cell is not part of the claimed composition. Therefore any prior art reference that relates to cell culture media and its use with cells in general is considered to be in the same field of endeavor as Applicant's claimed invention. Chachques, Furcht, Valerio and Wilson provide teachings that are drawn to the maintenance of cells for the purpose of cell therapy and are properly combined for their contributions to the field of cell therapy in general.

Applicant argues that the media contemplated by Valerio is a transduction media and adds factors in order to potentiate gene transfer and is thus relates to a different field of art, thereby belong to a different technical field to that of the present application.

This is not found persuasive because Valerio also teaches the use of a culture media for the maintenance of stem cells and it is this media composition that the obviousness rejection is referring to. In addition, the transitional phrase "comprising" in the claimed invention is open ended and allows for other components to be present in the composition.

In response to applicant's argument that Valerio is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, any reference that discloses a cell culture media that can be used for the maintenance of cells or a teaching with regard to cell growth or maintenance is considered to be in the same technical field as Applicant's claimed invention and thus suitable as prior art.

Applicant argues that those skilled in the art would not be reasonable led to take the teachings of Valerio and modify them with the teachings of Wilson. Applicant asserts that because Valerio uses protamine to increase the rate of gene transfer that one of ordinary skill in the art would not add heparin as this would render the teachings of Valerio invalid for its intended use because the heparin would neutralize the protamine.

This is not found persuasive because Wilson et al teach that FGF combined with heparin stimulates the growth of bone marrow cells such as those cultured by Valerio and one of ordinary skill in the art could have avoided any problems with neutralization of protamine by adding the heparin later in the culture period after the gene transfer had

taken place. Modifying the timing of the addition of supplements in order to gain their reported benefits is matter of routine optimization and experimentation for the artisan of ordinary skill in the art of cell culture.

Applicant argues that bone marrow cells do not express the surface marker of the muscle lineage CD56 unless they are carcinogenic. Since carcinogenic cells may not be used for cell transplantation, Applicant asserts that the combination of Valerio and Wilson would again be contrary to conventional knowledge to those skilled in the art.

This is not found persuasive because the cells used by Applicant are not a part of the claimed composition that is under examination. Just because Applicant uses the claimed composition with a different cell type does not mean that the composition can be used to culture other cell types as well (as shown by the prior art below). Putting the cell type in the preamble as part of the intended use would NOT change the composition as well as the patentability of the composition is based on its structural features and not its intended use.

According to M.P.E.P. § 2111, the pending claims must be given their broadest reasonable interpretation consistent with the specification. Broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In *In re Prater* (citations omitted), the court ruled that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which

have no express basis in the claim. The court found that applicant was advocating the latter, i.e., the impermissible importation of subject matter from the specification into the claim.

Therefore Applicant's disclosure with regard to the methods of using the claimed media composition are NOT to be imported into the claims of the elected invention of the culture media composition.

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Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-40 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites the limitations of “between 0.1 and 10.000 UI/ml heparin; between 0.1 and 10.000 UI/ml protamine” in lines 4 and 5 of the claim. Since the prior art measures protamine in concentration units of mg/ml which is contrary to Applicant’s disclosure of UI/ml the metes and bounds of the claim are unclear as one of ordinary skill in the art measures these compounds differently.

Appropriate correction and clarification is required.

Because claims 32-40 depend from indefinite claim 31 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al (The Journal of Immunology,2002).

Claim 31 is drawn to an autologous culture medium of autologous human progenitor stem cells, comprising: a) between 0.1% and 90% of autologous human serum; b) between 0.1 and 10.000 UI/ml heparin; c) between 0.1 and 10.000 UI/ml protamine; and d) a base culture medium including basic nutrients.

Dependent claims include the treatment of the autologous serum, the source of the autologous serum, the method of producing the autologous serum and the inclusion of an antibiotic.

Claims 33-35 are product-by-process claims. M.P.E.P. § 2113 reads, "Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps."

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)

The use of 35 U.S.C. §§ 102 and 103 rejections for product-by-process claims has been approved by the courts. "[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Xia et al teach a media composition that comprises AIM-V medium containing 2% autologous serum, 25 U/ml heparin and 0.125 mg/ml protamine sulfate (page 1134, figure 5, formula C). The AIM-V media inherently contains the claimed antibiotics streptomycin and gentamycin as well as basic nutrients for cell culture. While the

reference is silent with regard to the method of producing the autologous serum, it appears that the claimed autologous serum and the reference autologous serum would be structurally the same. Therefore the limitation of the autologous serum is deemed to be met by the reference. However, even if this were not the case, obtaining autologous human serum from the blood of the patient by means of plasmapheresis is a well established and conventional procedure and therefore obvious. As far as the Examiner can tell, the concentrations of the heparin and the protamine are reasonably close to the claimed concentrations that one of ordinary skill in the art would have been motivated with a reasonable expectation of success to lower the concentration of the heparin or the protamine upon duplicating the experiment of Xia et al in order to conserve resources and lower costs. While the Xia et al reference uses the media composition for a different purpose, as long is there is a motivation and reasonable expectation of success to arrive at the same concentrations as claimed by Applicant, the claimed composition is obvious. The treating of the autologous serum to inactivate a complement is also obvious as heat inactivation of serum is a well established and conventional procedure in the art of tissue culture (as acknowledged by Applicant on pages 3-4 paragraph 21).

Therefore the teaching of Xia et al renders obvious Applicant's invention as claimed.

Claims 31-40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chachques (US 2002/0124855) in view of Furcht et al (US 7,015,037), Duggins (US 4,735,726) and Yang et al (US 6,624,141).

Claim 38 is drawn to the medium of claim 31, further comprising at least one of amphoterycin B and a Fibroblast Growth Factor (FGF).

Claim 39 is drawn to the medium of claim 31, and comprises: 89% HAM-F12; 10% autologous human serum of a patient supplemented with heparin between 0.1 and 100 UI/ml and protamine between 0.1 to 100 UI/ml; and 1% penicillin/streptomycin.

Claim 40 is drawn to the culture medium of claim 39, wherein the autologous human serum further comprises at least one of 0.25 mg/ml of amphoterycin B and 0.1 to 250 pg/ml of recombinant bFGF.

Chachques describes a culture medium comprising 79% Ham-F12 medium, 25 pg/ml bFGF, 20% fetal calf serum and 1% penicillin/streptomycin (page 3 para 40). The medium is intended to be used to culture myogenic cells for the repair of a damaged myocardium. Autologous cells are preferred in order to reduce the immune response (page 2 para 23-24).

Chachques does not teach the use of autologous human serum, heparin, protamine or the specific concentrations as claimed by Applicant.

Furcht et al teach a method of culturing cardiomyocytes to be used to treat cardiac diseases such as cardiomyopathy (disorder of the myocardium) (column 9 lines 30-34). The cells can either be maintained in the presence of fetal calf serum or autologous serum (column 15 lines 39-41).

Therefore one of ordinary skill in the art would have been motivated to use autologous serum in the culture medium of Chachques given that Chachques emphasizes the importance of avoiding an immune response by using autologous cells and Furcht et al also teaches that cardiac cells can be cultured with autologous serum as well as fetal calf serum. One of ordinary skill in the art would have had a reasonable expectation of success because both Chachques and Furcht et al were culturing cardiac cells for the treatment of a damaged myocardium.

Furcht et al is silent with regard to the method of collecting the autologous serum from the patient.

Duggins teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media (background, column 1 lines 28-32).

Yang et al teach that heparin is a coagulant of choice particularly in all procedures involving extracorporeal blood circulation such as plasmapheresis (background, column 1 lines 25-35). Protamine is used to neutralize the negative side-effects of heparin and Yang et al teach a specific protamine that is bioactive and has low toxitcity (column 3 lines 45-55).

Therefore one of ordinary skill in the art would have been motivated with a reasonable expectation of success to use plasmapheresis to obtain autologous serum for the culture medium of Chachques because Duggins teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media. One of ordinary skill in the art would have also been motivated to use heparin as the anticoagulant in the plasmapheresis method as Yang et al teach that it is commonly

known in the art to do so. One of ordinary skill in the art would have been motivated to use the specific protamines described by Yang et al in the plasmapheresis method as Yang et al teaches that they neutralize the negative side-effects of heparin and are bioactive and have low toxicity. Applicant has disclosed that the use of heparin and protamine in a plasmapheresis method would have provided an autologous serum with roughly the same amounts (or similar) of heparin and protamine in the serum as claimed by Applicant (Specification page 5 para 28). The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The concentrations of the ingredients in the culture medium would have been a matter of routine optimization and experimentation, the artisan of ordinary skill recognizing that the growth of the cells and the success of their therapeutic application would be affected by these concentrations and thus be result-effective variables.

Therefore the combined teachings of Chachques, Furcht et al, Duggins and Yang et al render obvious Applicant's invention as claimed.

Claims 31-40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (US 6,472,212) in view of Wilson et al (US 5,817,773).

Valerio et al describe methods and compositions for culturing primate bone marrow cells, specifically including human cells (column 26 example d). A media

composition is described that comprises a base culture medium that includes basic nutrients, 5% heat inactivated autologous human serum, 4 µg/ml protamine sulfate and 100 U/ml penicillin (column 29 lines 33-40). Many different types of culture media are taught to be suitable and commercially available and a short non-restricted list is mentioned. While Ham-F12 is not on that list, it is a media known in the prior art to be used for culturing bone marrow cells and would have been an obvious alternative. The serum amounts are taught to vary from 5 to 30% and the media compositions are taught to include one or more antibiotics as well as growth factors (column 14 lines 57-63). Streptomycin is indicated as an acceptable antibiotic for inclusion in the media composition with penicillin as well (column 24 line 44).

Valerio et al do not specifically include heparin or fibroblast growth factor (FGF) in the media composition.

Wilson et al teach the stimulation of hematopoietic cells with fibroblast growth factor (FGF). An FGF is also taught to be used in combination with other growth factors (column 12 lines 20-25). Heparin sulfate is taught to be used to potentiate the stimulatory effect of concentrations of an FGF administered to hematopoietic cells (column 12 lines 63-66). Addition of at least one FGF in combination with heparin to a bone marrow cell culture is taught to increase the numbers of stem cells in a population to be used for transplantation (column 17 lines 25-30). Recombinant FGFs are taught to be used as well (column 17 lines 37-62). Low concentrations of bFGF (0.2 ng/ml which is equal to 200 pg/ml) are taught to significantly enhance cell growth (column 22 lines 41-43) especially when combined with low concentrations of heparin.

Therefore one of ordinary skill in the art would have been motivated to add FGF with heparin to the media of Valerio et al because Wilson et al teach that FGF combined with heparin stimulates the growth of bone marrow cells. One of ordinary skill in the art would have had a reasonable expectation of success because both Valerio et al and Wilson et al were culturing bone marrow cells for therapeutic administration to humans.

The concentrations of the FGF and the heparin in the culture medium would have been a matter of routine optimization and experimentation, the artisan of ordinary skill recognizing that the growth of the cells, the success of their therapeutic application and the cost of the procedure would be affected by these concentrations and thus be result-effective variables.

Therefore the combined teachings of Wilson et al and Valerio et al render obvious Applicant's invention as claimed.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg